Author's response to reviews

Title: Intrafamilial phenotypic heterogeneity in a Taiwanese family with MAPT p.R5H mutation: a case report and literature review

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Author’s response to reviews:

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Kuo-Hsuan Chang, MD, PhD
BMC Neurology, Editor-in-Chief

RE: NURL-D-17-00282 (revised version 1),

Intrafamilial phenotypic heterogeneity in a Taiwanese family with MAPT p.R5H mutation: a case report and literature review

Dear Dr. Chang:

We would like to thank the reviewers for their helpful comments. Enclosed please find our revised manuscript. We have addressed the reviewers’ suggestions point-by-point as follow:

Reviewer 1: In this paper the authors describe the clinical features of a Taiwanese family displaying FTD, corticobasal degeneration (CBD), ALS and persistent depressive disorder (PDD) and highlighting the marked intrafamilial phenotypic variability and the association with a mutation in the MAPT gene p.R5H.

The paper is clear and the discussion is in agreement with the results.
Question 1: I suggest to screen the c.14G>A (p.R5H) variant a cohort of Taiwanese age-matched controls and/or to report data form SNP databases concerning the Chinese population.

Reply: We thank the reviewer for the helpful suggestions. We have checked the frequency of this variant from the single whole genome sequencing (WGS) database enrolling 997 Taiwanese people from Taiwan Biobank https://www.twbiobank.org.tw/new_web/index.php. This substitution was absent in the WGS data of 997 Taiwanese subjects. It was also un-identified in more than 100 control Japanese subjects from previous studies (Hayashi S et al., Ann Neurol. 2002;51:525-30.), we therefor hypothesize that this variant is not a common polymorphism in the Asian population

This point has been addressed in the “Case Presentation”, page 9, lines 11-13; page 10, lines 8-10; “Discussion”, page 11, the bottom lines and page 12, lines 1-2.

Question 2: Discussion: I would add that MAPT mutations have also been found in pure motor neuron degeneration (Neurology. 2014 Jun 3;82(22):1990-8. doi: 10.1212/WNL.0000000000000476)

Reply: We thank the reviewer for the comments. We have added that MAPT mutations have also been found in a large Italian kindred with pure motor neuron degeneration (Neurology. 2014 Jun 3;82(22):1990-8.) suggested by the reviewer as below.

MAPT p.D348G mutation was found in a large Italian kindred with pure lower motor neuron degeneration, implicating tau degradation pathway defects in motor neuron degeneration.

This sentence has been addressed in the “Discussion” section, Page 11, lines 15-17.

Question 3: Conclusion: Please revise the sentence as follows:

In summary, we present the first Taiwanese family presenting with PPA variant of FTD, CBD, ALS and PDD and carrying a MAPT p.R5H mutation. Our findings contribute to highlight the marked phenotypic variability within subjects with the same MAPT mutation and specifically extend the current knowledge of phenotypes associated to MAPT p.R5H mutation.

Reply: We thank the reviewer for the kind corrections. This sentence has been revised according to the reviewer’s suggestions and was addressed in the lines 1-5 on page 15.

Reviewer 2: The manuscript by Lin et al examined the pathogenic mutations of the MAPT gene in a patient with frontotemporal degeneration. The authors found a c.14G>A (p.R5H) mutation in a Taiwanese FTD family. However, the symptoms and signs are different among the patients in the family. And his siblings do not showed any neurological symptoms. Collectively, this paper includes no novel finding so far.
Reply: We thank the reviewer for the comments. In this study, we present the first Taiwanese family presenting with PPA variant of FTD, CBD, ALS and PDD and carrying a MAPT p.R5H mutation. Our findings contribute to highlight the marked phenotypic variability within subjects with the same MAPT mutation and specifically extend the current knowledge of phenotypes associated to MAPT p.R5H mutation.

Reviewer 3: Lin et al. present a case of a patient presenting with symptoms of a neurodegenerative disorder out of the spectrum of frontotemporal dementia associated with a very uncommon mutation in exon 1 of the MAPT gene, that, reportedly, has been demonstrated in only 2 Japanese families so far.

This report is - with the exception of some minor elisions - well written supported by a useful set of diagnostic data. Its strength is delineating genotype - phenotype heterogeneity as well as the general complexity of the phenotype of the FTD-spectrum. I recommend acceptance of the article after some minor revisions. The final form should be corrected for some orthographic omissions, and may be formally revised/resubmitted once.

Question 1: Please add results of lumbar puncture including markers of dementia if available.

Reply: We thank the reviewer for the comments. However, because the patient hesitated about the lumbar puncture examination, we didn’t have the chance to access the levels of total and phospho-tau proteins of cerebrospinal fluid.

This point has been addressed in the “Case Presentation” section, page 8, lines 5-7.

Question 2: Orthographic:

Abstract:

- You wrote: Overlapped

  Please write: overlapping

- You wrote: As mostly reported pathogenic mutations in MAPT occur in exons 9-13, few families are reported outside of this region.

  Please write: While most reported pathogenic mutations in MAPT occur in exons 9-13, few families have been reported with mutations outside of this region.

- You wrote: Our findings extended the current knowledge of phenotypic heterogeneity among members of family carrying MAPT p.R5H mutation.

  Please write: Our findings extend the current knowledge of phenotypic heterogeneity among members of families carrying MAPT p.R5H mutation.
Background:

- You wrote: …..including FTD, corticobasal degeneration (CBD), ALS and persistent depressive disorder (PDD).

  o Please write: ….. including symptoms of FTD, corticobasal degeneration (CBD), ALS and persistent depressive disorder (PDD).

Case presentation:

- You wrote: A 63-year-old right-handed man, who has underlying medical conditions of hypertension and hyperlipidemia with well control,…. 

  o Please write: A 63-year-old right-handed man, with underlying well controlled arterial hypertension and hyperlipidemia …. 

- You wrote: … limited eye-of-movement…

  o Please write:

- Please transfer the sentence: "Neurological examinations showed a mask face, right-hand apraxia, bradykinesia and rigidity. There was stimulus-sensitive myoclonus on his right hand and forearm." Directly after …. "and he could not perform delicate movements with his right hand."

- You wrote: Among his family, the mother of patient had been diagnosed with ALS at the age of 60 (Figure 2).

  o Please write: Among his family, the mother of the patient had been diagnosed with ALS at the age of 60 (Figure 2).

Discussion:

- You wrote: As previously studies have shown that FTD, CBS, PSP, and motor neuron disorders are regarded as a clinically and biologically cohesive spectrum of tauopathy, although the neuronal inclusions exhibit distinct differences isoforms of tau deposition, clinical association of FTD and motor neuron disorders is not an exceptional occurrence, and there was 5% of FTD patients with motor neurons disorders under observation

  o Please write: As previous studies have shown that FTD, CBS, PSP, and motor neuron disorders are regarded as a clinically and biologically cohesive spectrum of tauopathy with neuronal inclusions exhibiting distinct isoforms of tau, clinical association of FTD and motor neuron disorders occurs in approximately 5% of FTD cases.

- You wrote: …and mother of the index patient had ALS…
Please write: … and the mother of the index patient had ALS….

You wrote: … which symptom had contributed to the delay of proper diagnosis and treatment of FTD.

Please write: … which contributed to the delay of proper diagnosis and treatment of FTD.

Reply: We gratefully thank the reviewer for the kind corrections of the grammars and wordings in this paper. We have corrected all the orthographic errors pointed by the reviewer accordingly.

Editor:

Thank you once again for giving us the opportunity to address the reviewers’ suggestions. We hope you would agree that with the revisions, the revised manuscript is much improved. The manuscript along with three figures was submitted according to the designated online submission process.

Yours truly,

Pei-Hao Chen, MD.

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